Remarks

Status of the Claims

Claims 26-38 are pending in the present application. Applicants have amended claims 26, 27 and 38. Support for these amendments can be found in the specification at least on page 6, lines 22-25; on page 25, lines 18-20; on page 10, lines 22-24; and from page 17, line 15 to page 18, line 6. Upon entry of the amendments, claims 26-38 will be pending in the application.

Formal Matters

In the Office action, the title was deemed not descriptive of the invention to which the elected claims are directed. Applicants have replaced the title and request that the objection to the title be withdrawn.

Claim Rejections Under 35 U.S.C. § 112, second paragraph

Claims 26 and 27 were rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite because the claims did not indicate an amount of fusion protein to be administered to a mammal. Claims 28-38 are rejected as depending from an allegedly indefinite claim. As recommended in the Office action, Applicants have amended claims 26 and 27 to include the phrase "an effective amount of." Accordingly, Applicants request that the claim rejections under 35 U.S.C. § 112, second paragraph, be reconsidered and withdrawn.

Claim Rejections Under 35 U.S.C. § 103(a)

Claims 26, 28-30, 34-36 and 38 are rejected under 35 U.S.C. § 103(a) over U.S. Patent No. 5,723,125 to Chang *et al.* ("Chang") in view of U.S. Patent No. 5,541,087 to Lo *et al.* ("Lo"). Claims 27, 31-33 and 37 are rejected under 35 U.S.C. § 103(a) over Chang and Lo, and in further view of U.S. Patent No. 5,116,964 to Capon *et al.* ("Capon"). Applicants respectfully traverse these rejections.

Applicants submit that the cited references do not render the claimed invention obvious because Chang teaches away the use of an Fc region derived from at least a portion of IgG1 and IgG3 chains. References cannot be combined where a reference teaches away from their combination (MPEP § 2145). Chang states that using the IgG4 chain as the Fc moiety is advantageous and preferred because "(unlike the γ1 chain) [the γ4 chain] avoids the wide spectrum of secondary biological properties, such as complement fixation and antibody-dependent cell-mediated cytotoxicity (ADCC)" (Chang, column 2, lines 21-23 and column 3, lines 63-67). In contrast, the invention of independent claims 26 and 27 relates to methods using a fusion protein comprising an immunoglobulin Fc region derived from at least a portion of an IgG1 chain constant region or at least a portion of an IgG3 chain constant region, each of which are known to possess these secondary biological properties. By teaching the disadvantages of using Fc moieties that mediate ADCC and complement fixation, Chang teaches away from the claimed invention. Therefore, Chang cannot be combined with the other cited references to render obvious the invention of independent claims 26 or 27 or of any of dependent claims 28-38, each of which depend directly or indirectly from claims 26 or 27.

Applicants further submit that the claimed invention is not obvious because it benefits from unexpected advantageous properties not possessed or described by the cited art. "The discovery of new and unobvious properties in the claimed compounds rebuts even a *prima facie* case of obviousness where the art is silent on that property." *In re Albrecht*, 514 F.2d 1389, 1394 (C.C.P.A. 1975). Similarly, where a 35 U.S.C. § 103 rejection is based on structural similarities, "evidence of unobvious or unexpected advantageous properties may rebut a *prima facie* case of obviousness." *In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987) (citing *In re Papesch*, 315 F.2d 381, 386-87 (C.C.P.A. 1963)).

The fusion protein of the claimed invention possesses the new and unobvious property of moderating effector functions upon binding to the IFN-α receptor by occluding the Fc residues that mediate ADCC and complement fixation. The fusion protein comprises, in an N- to C-terminal direction, an immunoglobulin Fc region derived from at least a portion of an IgG1 or IgG3 chain, and an IFN-α protein. Applicants have discovered that by placing the Fc region at

the N-terminus of the fusion protein, the peptide is able to moderate effector functions upon binding to the IFN-α receptor. In particular, when the IFN-α binds to its receptor on a cell surface, "the orientation of the Fc region is altered and the sequences that mediate antibody-dependent cell-mediated cytotoxicity (ADCC) and complement fixation appear to be occluded" (Application, page 10, lines 12-14). Consequently, the Fc region of the fusion protein does not mediate ADCC or complement fixation effectively (Application, page 10, lines 14-15). Applicants submit that prior art IFN-α fusion proteins did not possess this property, conferred by the specific N- to C- terminal orientation of the fusion protein subunits used in the claimed method, and that the art did not appreciate that occlusion of ADCC and complement fixation sequences would result from the changed orientation.

The art also failed to appreciate the advantages of using a fusion protein that benefits from this unexpected property. Specifically, the Fc region can include wild-type Fc regions derived from IgG1 and IgG3 chains, which mediate Fc receptor binding, but would otherwise cause deleterious effects from ADCC and complement fixation. The high affinity for the Fc receptor exhibited by IgG1 and IgG3 generates an advantageous tissue distribution when the claimed fusion protein is used for treating a mammal. For example, "there is a high level of Fc gamma receptor in the liver, which is the site of infection by the viruses causing hepatitis B and hepatitis D" (Application, page 26, lines 4-6). As such, the fusion protein can be preferentially targeted to the virus-infected tissue, thus reducing side-effects caused by the presence of IFN-α in other tissues (Application, page 8, line 25 to page 9, line 1).

Thus, Applicants have discovered a new and unobvious property of the novel fusion proteins used in the claimed invention and have discovered the advantages of this property in methods of treating a condition alleviated by the administration of IFN-α. Applicants submit that the art is silent about the newly discovered advantages of the claimed methods. Under *In re* Albrecht, the discovery of a new and unobvious property about which the art is silent rebuts even a *prima facie* case of obviousness. Applicants therefore submit that the cited references cannot render the claimed methods obvious.

Based on the foregoing arguments, Applicants submit that the cited references do not render obvious the invention of claim 26 or of the other pending claims, which depend directly or indirectly from claim 26. Accordingly, Applicants respectfully request that the rejection of the pending claims under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

CONCLUSION

Claims 26-38 are pending and believed to be in condition for allowance. Examiner Jiang is invited to telephone the undersigned agent to discuss any remaining issues.

Respectfully submitted,

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